UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,757	06/06/2005	Zhi-Cheng Xiao	0380-P03638US0	5465

110 7590 01/16/2007

DANN, DORFMAN, HERRELL & SKILLMAN
1601 MARKET STREET
SUITE 2400
PHILADELPHIA, PA 19103-2307

EXAMINER	
DUTT, ADITI	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,757	XIAO, ZHI-CHENG	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 16-26* is/are pending in the application.

4a) Of the above claim(s) *5,6 and 17-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-9 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-9 and 16-26* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 June 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 15 November 2006 has been entered in full.

Election with traverse

2. Applicant's election with traverse of Group I, claims 1-4, 7-9 and 16, in the reply filed on 15 November 2006 is acknowledged.

3. The traversal is on the ground(s) that: (i) the interaction of Nogo with Caspr, and the implication of this interaction in myelination, comprises a special technical feature that imparts unity of invention to all the claims; (ii) failure to "assert separate classification as warranting the present restriction requirement"; (iii) the subject matter of all the claims was treated as a single invention in the international stage of the application. The Applicant further asserts that because there exists a single inventive concept, a complete search of any one of the nine claim groups would encompass the same art, thereby "should not materially affect the examiner's workload". This is not found persuasive, because as explained in the previous Office Action (dated 11 October 2006, pages 3-4), the special technical feature of Group I is a composition comprising Nogo and Caspr, and using the composition for stimulating myelination of an axon, which is not required by the other products or methods of the other Groups.

4. Furthermore, the methods of inventions IV-IX, have a special technical feature and are restricted properly, as they are they are practiced with materially different process steps for materially different purposes and each requires a non-coextensive search because of different starting materials, process steps, and goals. Additionally, the defining compounds comprising the compositions (e.g. Nogo and Caspr, Nogo and Caspr mimetic, and substance promoting interaction of Nogo and Caspr) of inventions I-III do not share a common structure or activity.

5. Furthermore, each patent application is examined on its own merits. That the invention was deemed to have unity by the PCT searching authority has no bearing on the national stage application that follows US practice. The claims in the national stage application can be restricted on the basis of lack of unity of invention at the discretion of the examiner. See 37 CFR 1.499. Lastly, it is to be noted that the restriction requirement in a national stage application is not based on separate classification of the inventive groups.

6. Applicant is reminded that, upon allowance, the first enabled method of using the claimed compound will be rejoined to the examined Invention. However, until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims should be maintained (*In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b), 1184 O.G. 86 March 26, 1996).

The requirement is still deemed proper and is therefore made FINAL.

7. Claims 5-6 and 17-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 15 November 2006.

8. Claims 1-4, 7-9 and 16, drawn to a composition comprising Nogo and Caspr, and a method of stimulating myelination of a neural axon, are being considered for examination in the instant application.

Drawings

9. The drawings are objected to because:

i) Figure 8B (Second Aspect) is missing

ii) Two different figures are identified as Figure 10B (Second Aspect – 21/42 and 22/42).

iii) Figure 11B (Second Aspect) does not have the 'B' label.

iv) The figures are not consecutively numbered.

10. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an

amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

11. The disclosure is objected to because of the following informalities:

A) Brief Description of the Drawings

Brief description for Figure 10B (Second Aspect - 22/42) is missing.

Appropriate correction is required.

B) Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The

following title is suggested: "NOGO AND CASPR COMPLEX USEFUL IN THE MYELINATION OF NEURAL AXON".

Appropriate correction is required.

C) Arrangement

Arrangement of the Specification

The drawings are not consecutively numbered in the specification. Following guidelines should be followed:

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.

Appropriate correction is required.

Claim Objections

12. Claims 1, 2, 7-9 and 16, are objected to because of the following informalities:

a) Regarding claims 1 and 9, acronyms "Caspr" and "CNS" recited should be spelled out in all independent claims for clarity. Appropriate correction is required.

b) Claims 1, 2, 7-9 and 16 recite non-elected species.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-Lack of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-4, 7-9 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

14. The specification does not reasonably provide enablement for a composition comprising Nogo and Caspr, including a composition formulated for direct injection *in vivo* into the CNS, and a method of stimulating myelination of a neural axon. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

15. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, include the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

16. The claims are drawn to a composition comprising Nogo and Caspr or, a complex between Nogo and Caspr, (claims 1 and 2), including Nogo-66 and Caspr1 (claims 3 and 4), formulated for direct *in vivo* injection into the central nervous system (CNS) (claims 7-9), and used in the method for stimulating myelination of a neural axon, by contacting the composition with a neuron or an oligodendroglial cell (claim 16).

17. The specification of the instant application teaches that the Nogo gene encodes an inhibitory myelin protein in rats and humans, and is important in the inhibition of axonal regeneration after injury (page 4, lines 32-34; page 5, lines 34-35). The specification further teaches that Nogo is expressed in three isoforms, Nogo-A, Nogo-B and Nogo-C, sharing the same extracellular 66-amino acid loop (Nogo-66) and encompassing mutants and variants (page 6, lines 15-17; page 13, 11-21), of which Nogo-A is the most extensively studied isoform important in the formation and maintenance of axoglial junction architecture (page 5, lines 34-35;

page 8, lines 33-35). The specification also teaches that Caspr (contactin-associated protein or paranodin) is a transmembrane protein, and encompasses 4 isoforms (Caspr-1, Caspr-2, Caspr-3 and Caspr-4), mutants and variants (page 7, lines 34-35; page 13, lines 23-30). Furthermore, the specification teaches that Nogo-A present in oligodendrocytes interacts directly with the axonal Caspr through the Nogo-66 loop (page 9, lines 1-5). Finally, the specification demonstrates the association of Nogo and Caspr, using Western Blot, and co-immunoprecipitation assays, (page 33, lines 2-4; Figure 3Bb; page 40, lines 10-13). The interaction of Nogo and Caspr is also demonstrated using membrane extracts of adult mouse brain, GST pull-down assays, wherein Caspr is pulled down by GST-Nogo-66 (page 35, lines 13-16; Figure 5Ab). However, the specification does not disclose any evidence or sound scientific reasoning that the limited information presented in the disclosure can be directly extrapolated to compositions comprising any form of Nogo and Caspr, including those formulated for direct injections in the CNS, and further that stimulate myelination of a neural axon *in vivo*. Undue experimentation would be required by one skilled in the art, to use such compositions as a pharmaceutical by direct injections into the CNS and stimulate myelination.

18. Relevant literature teaches that Nogo has 3 isoforms that arise from alternative promoter and splicing (Woolf, Neuron 38: 153-156, 2003; page 153, column 2, para 3). Woolf further teaches that Nogo-A possesses a

long N-terminal extension, that promotes inhibition of axonal growth *in vitro* (page 154, column 1, para 2), via the Nogo-66 receptor (Wang et al., Jour Neurosc 22: 5505-5515, 2002; page 5505, column 2, para 2). Mingorance et al., teach that Nogo-A is the longest isoform encoded by the Nogo gene (RTN4) (Mol Cell Neurosc 26: 34-49, 2004). Furthermore, the art teaches that Nogo-A clusters are disrupted in the demyelination rodent models (Teng et al., J Neurochem 89: 801-806, 2004). However, relevant prior and post art literature does not teach pharmaceutical compositions comprising any form of Nogo and Caspr, directly injected into the CNS, and further stimulating myelination *in vivo* by contacting the composition with a neuron or oligodendroglial cell. The only disclosed use is for the stimulation of myelination, and there is no guidance to indicate that this could be done by one skilled in the art.

19. Furthermore, the term "pharmaceutical" in claims 7-9 and 16 implies a therapeutic use. However, the specification does not provide enablement for a pharmaceutical composition comprising any form of Nogo and Caspr, including those to be directly injected in the CNS for stimulation of myelination. The specification does not teach how to use a Nogo and Caspr, or a complex between Nogo and Caspr, formulated in a pharmaceutical composition, and used for the stimulation of myelination *in vivo* without undue experimentation. There are no methods or working examples directed to the administration of pharmaceutical composition for the treatment of a disorder. Relevant literature states that Caspr is

expressed in the unmyelinated axon and gets localized to the paranodal junctions soon after the onset of myelination (Rios et al., J Neurosc 20: 8354-8364, 2000; page 8354, column 2, para 2). Furthermore, Karnezis et al., teach that mice vaccinated against Nogo, block the neurite inhibitory activity *in vitro* (Nature Neurosc 7: 736-744, 2004; page 741, Figure 6c); and suppresses clinical signs in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS) (page 742, Figure 7). However, the prior art literature as stated above only teaches *in vitro* experiments to demonstrate the biological and therapeutic effects. The literature and instant specification do not teach *in vivo* studies to demonstrate therapeutic implications of the claimed pharmaceutical composition in specific disorders. *In vitro* experiments such as that described in the instant application, are vastly different from *in vivo* assays, both physiologically or biologically, and in predictability of success, and thus would entail undue experimentation by a skilled artisan (See *Maas*, 9 USPQ2d 1746). As acknowledged in the instant specification, "myelination is a complex multistep process where the underlying molecular mechanism remains far from being completely defined" (page 48, lines 28-29), the implied therapeutic use of Nogo and Caspr, or the complex between Nogo and Caspr, formulated into a pharmaceutical composition, and stimulating myelination, would involve undue experimentation of one skilled in the art in vivo.

20. Due to the large quantity of experimentation necessary for a pharmaceutical composition comprising any form of Nogo and Caspr, and stimulating myelination in vivo by CNS injection; absolute lack of direction/guidance presented in the specification regarding the same; the complex nature of the invention; the state of the prior and post art which has yet to determine *in vivo* effects of Nogo and Caspr complex injections and, the unpredictability of extrapolating the *in vitro* effects *in vivo*; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112-Written description

21. Claims 1-3, 7-9 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

22. The claims are drawn to a composition comprising Nogo and Caspr or, a complex between Nogo and Caspr, (claims 1 and 2), including Nogo-66 (claim 3), formulated for direct *in vivo* injection into the central nervous system (CNS) (claims 7-9), and used in the method for stimulating myelination of a neural axon, by contacting the composition with a neuron or an oligodendroglial cell (claim 16).

23. The specification of the instant application teaches that Nogo is expressed in three isoforms, Nogo-A, Nogo-B and Nogo-C, sharing the same extracellular 66-amino acid loop (Nogo-66) and encompasses mutants and variants (page 6, lines 15-17; page 13, 11-21), of which Nogo-A is the most extensively studied isoform important in the formation and maintenance of axoglial junction architecture (page 5, lines 34-35; page 8, lines 33-35). The specification also teaches that Caspr (contactin-associated protein or paranodin) is a transmembrane protein, and encompasses 4 isoforms (Caspr-1, Caspr-2, Caspr-3 and Caspr-4), mutants and variants (page 7, lines 34-35; page 13, lines 23-30). Furthermore, the specification teaches that Nogo-A present in oligodendrocytes interacts directly with the axonal Caspr through the Nogo-66 loop (page 9, lines 1-5). Additionally, the specification demonstrates the association of Nogo and Caspr, using Western Blot, and co-immunoprecipitation assays, (page 33, lines 2-4; Figure 3Bb; page 40, lines 10-13). The interaction of Nogo and Caspr is also demonstrated using membrane extracts of adult mouse brain, GST pull-down assays, wherein Caspr is pulled down by GST-Nogo-66 (page 35, lines 13-16; Figure 5Ab). However, the brief description in the specification of one example of Nogo (Nogo-A), and one example of Caspr (Caspr1), is not adequate written description of an entire genus of Nogo and an entire genus of Caspr. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient

distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. However, in this case, the specification has not shown a relationship between the structure and function of the claimed genus of Nogo or Caspr.

24. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

25. The skilled artisan cannot envision the genus of Nogo or Caspr of the encompassed composition and methods involving such, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

26. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to

mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

27. Therefore, only compositions comprising Nogo-A and Caspr1, and methods utilizing such composition, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

28. No claims are allowed.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

31. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is

available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
28 December 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER